

1. (Amended three times) A method of identifying a compound that binds to a coactivator binding site of a nuclear receptor, said method comprising:

C modeling test compounds that fit spatially into the nuclear receptor coactivator binding site using an atomic structural model of the nuclear receptor coactivator binding site or portion thereof; and

screening said test compounds in an assay that measures binding of a test compound to the nuclear receptor coactivator binding site, thereby identifying a test compound that binds to the coactivator binding site of said nuclear receptor.

2. (Amended twice) The method of claim 1, wherein said atomic structural model comprises atomic coordinates of amino acid residues identified by homology alignment with residues of a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53) selected from the group consisting of Val284, Phe293, Ile302, Leu305, and Leu454.

C<sup>2</sup> 3. (Amended twice) The method of claim 1, wherein said atomic structural model comprises atomic coordinates of amino acid residues identified by homology alignment with residues of a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53) selected from the group consisting of Val284, Lys288, Ile302, Lys306, Leu454 and Glu457.

4. (Amended twice) The method of claim 1, wherein said atomic structural model comprises atomic coordinates of amino acid residues identified by homology alignment with helix 3 residues Ile280, Thr281, Val283, Val284, Ala287, and Lys288, helix 4 residue Phe293, helix 5 residues Gln301, Ile302, Leu305, Lys306, helix 6 residue Cys309, and helix 12 residues Pro453, Leu454, Glu457, Val458 and Phe459 found in a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53).

5. (Amended twice) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Ile280, Thr281, Val283,

Val284, Ala287, and Lys288, helix 4 residue Phe293, helix 5 residues Gln301, Ile302, Leu305, Lys306, helix 6 residue Cys309, and helix 12 residues Pro453, Leu454, Glu457, Val458 and Phe459 found in a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53).

6. (Amended twice) The method of claim 5, wherein said amino acid residues identified by homology alignment with residues of a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53) comprise Val284, Phe293, Ile302, Leu305, and Leu454.

C<sup>2</sup> cont  
7. (Amended twice) The method of claim 5, wherein said amino acid residues identified by homology alignment with residues of a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53) comprise Val284, Lys288, Ile302, Lys306, Leu454 and Glu457.

8. (Amended twice) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with helix 3 residues Ile280, Thr281, Val283, Val284, Ala287, and Lys288, helix 4 residue Phe293, helix 5 residues Gln301, Ile302, Leu305, Lys306, helix 6 residue Cys309, and helix 12 residues Pro453, Leu454, Glu457, Val458 and Phe459 found in a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53).

C<sup>3</sup>  
12. (Amended twice) The method of claim 1, wherein said assay is an *in vivo* assay.

C<sup>4</sup>  
15. (Amended) The method of claim 14, wherein said test compound is a small organic molecule, a peptide, or a peptidomimetic.

Please add new Claims 32 – 43.

C<sup>5</sup>  
32. (New) The method of claim 14 wherein the agonist promotes hormone-dependent coactivator binding to the receptor.

33. (New) The method of claim 14 wherein the antagonist blocks hormone-dependent coactivator binding to the receptor.

34. (New) The method of claim 1, wherein said atomic structural model comprises atomic coordinates of amino acid residues identified by homology alignment with helix 3 residues Leu354, Val355, Met357, Ile358, Ala361, and Lys362, helix 4 residue Phe367, helix 5 residues Gln375, Val376, Leu379, Glu380, helix 6 residue Trp383, and helix 12 residues Asp538, Leu539, Glu542, Met543 and Leu544 found in a portion of human estrogen alpha receptor (SEQ ID NO: 56, SEQ ID NO: 57 or SEQ ID NO: 60).

35. (New) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Leu354, Val355, Met357, Ile358, Ala361, and Lys362, helix 4 residue Phe367, helix 5 residues Gln375, Val376, Leu379, Glu380, helix 6 residue Trp383, and helix 12 residues Asp538, Leu539, Glu542, Met543 and Leu544 found in a portion of human estrogen alpha receptor (SEQ ID NO: 56, SEQ ID NO: 57 or SEQ ID NO: 60).

36. (New) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Ile238, Ile239, Ile241, Val242, Ala245, and Lys246, helix 4 residue Phe251, helix 5 residues Gln259, Ile260, Leu263, Lys264, helix 6 residue Cys267, and helix 12 residues Pro410, Leu411, Glu414, Met415 and Leu416 found in a portion of human retinoid receptor hRAR $\gamma$  (SEQ ID NO: 34 and SEQ ID NO: 35).

37. (New) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Leu276, Phe277, Leu279, Val280, Ala283, and Lys284, helix 4 residue Phe289, helix 5 residues Gln297, Val298, Leu301, Arg302, helix 6 residue Trp305, and helix 12 residues Thr449, Phe450, Glu453, Met454 and

Leu455 found in a portion of human retinoid receptor hRXR $\alpha$  (SEQ ID NO: 36 and SEQ ID NO: 37).

38. (New) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Val291, Glu292, Ile294, Thr295, Ala298, and Lys299, helix 4 residue Phe304, helix 5 residues Gln312, Val313, Leu316, Lys317, helix 6 residue Val320, and helix 12 residues Pro465, Leu466, Glu469, Ile470 and Tyr471 found in a portion of human peroxisome receptor hPPAR $\gamma$  (SEQ ID NO: 36 and SEQ ID NO: 37).

39. (New) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Ile238, Glu239, Val241, Ile242, Ala245, and Lys246, helix 4 residue Phe251, helix 5 residues Gln259, Val260, Leu263, Lys264, helix 6 residue Ala267, and helix 12 residues Pro416, Leu417, Glu420, Val421 and Phe422 found in a portion of human vitamin D receptor hVDR (SEQ ID NO: 40 and SEQ ID NO: 41).

40. (New) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Val571, Ile572, Ala574, Val575, Ala578, and Lys579, helix 4 residue Phe584, helix 5 residues Gln592, Met593, Leu596, Gln597, helix 6 residue Trp600, and helix 12 residues Glu751, Met752, Glu755, Ile756 and Ile757 found in a portion of human glucocorticoid receptor hGR (SEQ ID NO: 44 and SEQ ID NO: 45).

41. (New) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Val726, Ile727, Ala729, Val730, Ala733, and Lys734, helix 4 residue Phe739, helix 5 residues Gln747, Met748, Leu751,

Gln752, helix 6 residue Trp755, and helix 12 residues Glu907, Met908, Glu911, Ile912 and Ile913 found in a portion of human progesterin receptor hPR (SEQ ID NO: 46 and SEQ ID NO: 47).

42. (New) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Met777, Ile778, Val780, Val781, Ala784, and Lys785, helix 4 residue Phe790, helix 5 residues Gln798, Ile799, Ile802, Gln803, helix 6 residue Trp806, and helix 12 residues Ala958, Met959, Glu962, Ile963 and Ile964 found in a portion of human mineralocorticoid receptor hMR (SEQ ID NO: 48 and SEQ ID NO: 49).

43. (New) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues selected from the group consisting of helix 3 residues Leu245, Val246, Val248, Val249, Ala252, and Lys253, helix 4 residue Phe258, helix 5 residues Gln266, Met267, Ile270, Gln271, helix 6 residue Trp274, and helix 12 residues Glu426, Met427, Glu430, Ile431 and Ile432 found in a portion of human androgen receptor hAR (SEQ ID NO: 50 and SEQ ID NO: 51).

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